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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,584	04/08/2004	Stephen Hart	20040117.ORI	6640

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,584	HART ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-26,31-33 and 39-41* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,9-11,17-26,31-33,40 and 41* is/are rejected.

7)☒ Claim(s) *12-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☑ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of: Group II (claims 2-11, 17-26, 31-33, and 40-41), and a further election of Group VI (claim 5), which reads on claims 5-6, 9-11, 17-26, 31-33 and 40-41, in the reply filed on 2-27-07 is acknowledged.

2. The traversal is on the ground(s) that the claims are sufficiently closely related that restriction should not be required and the applicants respectfully request that the requirement be withdrawn. This is particularly true with respect to the linking nature of claims 1 and 2 and it is not believed that the examination of all the claims would put an undue burden on the Examiner in searching the relevant art. This is not found persuasive because as set forth in the prior Office Action Groups I-VI do not appear to share a special technical feature that makes a contribution over the prior art since the teachings of Buluwella et al. discloses methods of suppression comprising the use of an effector comprising a complex featuring HDAC. Additionally, the various methods recited in Groups I-VI, the inventions relate to multiple methods that involve distinct objectives, distinct method steps, distinct materials, and producing distinct outcomes. The multiple methods are therefore considered to encompass multiple categories of invention. The claims are therefore not considered to have unity of invention as per 37 CFR 1.475(b)-(c).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 3-4, and 39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2-27-07.

4. Claims 12-16 were objected to in the Office Action mailed 1-11-2007, however Applicants did not reply to the grounds for objection. Therefore, Claims 12-16 remain objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim for the reasons of record. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

5. Claims 1-2, 5-6, 9-11, 17-26, 31-33 and 40-41 are presently under examination.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 22. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Oath/Declaration

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

There are alterations to the Citizenship, and Address of inventor Vainikka, however there are no initials accompanying the alteration.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 5-6, 9-11, 17-26, 31-33 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for suppressing the expression of a selected gene in a cell *in vitro,* or for modulating the expression of a selected gene in a cell *in vitro*, comprising introducing into the cell a molecule comprising a nucleic acid binding portion and a polypeptide or peptidomimetic repressor portion, wherein said repressor is all or a portion of a component of a histone acetyltransferase, does not reasonably provide enablement for practicing the claimed methods *in vivo* in a human subject with the production of a therapeutic effect as a result of practicing the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

© The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

The breadth of the claimed invention encompasses methods of medical treatment, including the treatment of cancers in which oncogenes play a role (see the bridging paragraph of pages 32-33). According to Applicant's specification, see page 32, beginning at line 14, the method of the claimed invention can be used to suppress or inactivate the expression of a gene whose expression it is desirable to suppress or inactivate. Such genes include oncogenes, viral genes including genes present in proviral genomes and so the method in relation to animals may constitute a method of medical treatment.

Example 8 of the specification as filed, applicants demonstrate the use of an oligo/peptide fusion molecule (ARP-L217) targeting the androgen receptor gene to greatly reduce the expression of androgen receptor in LNCap cells in comparison with those treated with control PBS solution. Examples 9-10 also demonstrate the use of

oligo/peptide fusion molecules to repress gene expression in LNCap human prostate tumor cells.

Example 6 is a prophetic example describing the use of the oligo/peptide fusion molecules of the present invention in a method for treating a patient, comprising delivering fusion molecules into cancer cells (see pages 53).

In regards to the therapeutic use of oligonucleotides *in vivo,* the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (Chirila et al., 2002; see abstract)." Chirila et al. page 327, last paragraph) teach that "[T]he in vivo delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs (oligonucleotides) in tissues," which is required to achieve therapeutic effects. As a conclusion to the review of Chirila et al., the state of oligonucleotide based drug therapy is summarized by the statement: "the antisense strategy only awaits a suitable delivery system in order to live up to its promise." Therefore, the efficacy of antisense based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide, to the appropriate tissues, and for a sufficient period of time, to produce the desired therapeutic effect. So far, it appears that all of the developments in antisense based therapies have not been sufficient to overcome this one basic obstacle, drug delivery. Furthermore, Applicant's specification does not provide actual working examples or guidance so that the skilled artisan can deliver the pharmaceutical compositions of the

claimed invention to target tissues successfully, to produce the desired therapeutic result without undue experimentation.

Jen et al. (*Stem Cells,* Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also concluded that "[a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." (See page 315, last two paragraphs).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "[A]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have

indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods in vivo in all organisms, with a resultant inhibition of gene expression and corresponding treatment effects, as claimed. Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense in vivo and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (i.e. the production of a therapeutic effect) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that an undefined target nucleic acid is inhibited and the desired secondary effect of treating tumors is obtained. The specification as filed provides does not specific guidelines for the full scope of compounds encompassed by these claims. The deficiencies in the

specification would constitute undue experimentation since these steps must be achieved without instruction from the specification before one is enabled to practice the claimed invention.

10. Claims 1-2, 5-6, 9-11, 17-26, 31-33 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

The instant claims are drawn to methods comprising the use of molecules comprising a nucleic acid binding portion and an expression repressor portion, or comprising a nucleic acid binding portion and a modifying portion. The claims further comprise wherein said molecule comprises wherein said modifying portion is a polypeptide or peptidomimetic which is capable of modulating covalent modification of nucleic acid or chromatin and is not an endonuclease, or wherein the modifying portion comprises a component of a histone acetyltransferase or all or a portion of a polypeptide that binds to or facilitates the recruitment of a histone acetyltransferase complex.

The scope of the instant claims reads on a broad genus of molecules comprising a variety of activities, however there is not clear structural correlation between the amino acid structures and/or nucleic acid sequence structures of the full scope of molecules of the instant invention, and the corresponding activities.

Example 8 of the specification as filed, applicants demonstrate the use of an oligo/peptide fusion molecule (ARP-L217) targeting the androgen receptor gene to greatly reduce the expression of androgen receptor in LNCap cells in comparison with those treated with control PBS solution. Examples 9-10 also demonstrate the use of oligo/peptide fusion molecules to repress gene expression in LNCap human prostate tumor cells. The specification as filed also describes the ARP-L218 oligo/peptide fusion, and a fusion between a triplex forming oligonucleotide and Sin3, a component of the histone deacetylation complex.

However, the specifically disclosed examples of the specification as filed is not representative of the full scope of molecules encompassed by the instant claims, such that the skilled artisan would be immediately apprised of the structures of the full scope of compounds having the asserted activities recited in the instant claims.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was

"ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

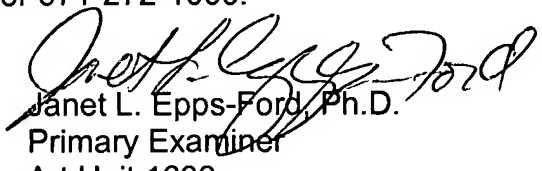
See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Due to the significant breadth of the instant claims, and the limited guidance provided in the specification as filed in regards to describing the structures of the full scope of compounds encompassed by the instant claims, the skilled artisan would have to resort to further experimentation in order to identify the full scope of compounds encompassed by the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Primary Examiner
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JLE